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CONDENSED ISOQUINOLINES. 34.* TRANSFORMATIONS OF 4H-THIENO-[3',2':5,6]- AND 4H-THIENO[2',3':5,6]PYRIMIDO-[1,2-*b*]ISOQUINOLINES

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Syntheses are given for previously unreported 4-chloro derivatives of 4H-thieno[3',2':5,6]- and 4H-thieno[2',3':5,6]pyrimido[1,2-b]isoquinolines and the reactions of these compounds with N- and S-nucleophiles were studied. The spectral characteristics and biological activity of the positional isomers were compared. The electron spectra most clearly reflect the differences related to the position of the sulfur atom in these quasiaromatic systems.

Keywords: derivatives of the 4H-thieno[3',2':5,6]- and 4H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinoline systems, positional isomers, nucleophilic substitution, calculation of biological activity.

Thienopyrimidines have long been the subject of chemical and biological research. The interest in these compounds is related to their broad range of biological activity, which is displayed by representatives of all the possible structural combinations of the thiophene and pyrimidine systems. Some thienopyrimidines display analgesic [2], antipyretic [3, 4], antiinflammatory [7-10], and anti-allergenic effects [5, 6, 11]. These compounds have been studied as antineoplastic agents [12] and for lowering the cholesterol level in the cardiovascular system [13, 14]. These findings have led us to continue our work on thienopyrimidine derivatives [15].

In the present work, we describe the chemical transformations of derivatives of 2,3-dimethyl-5,11-dihydro-4H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinoline-4,11-dione (**1**) and 5,11-dihydro-4H-thieno[2',3':5,6]pyrimido-[1,2-*b*]isoquinoline-5,11-dione (**2**) at the lactam fragment. These systems differ in the position of the heteroatom and we were interested in finding representatives displaying the greatest differences. We also sought to evaluate the effect of different functional groups on the electronic structure of the complex tetracyclic system. Such studies have been reported previously only for monocyclic systems [16-18].

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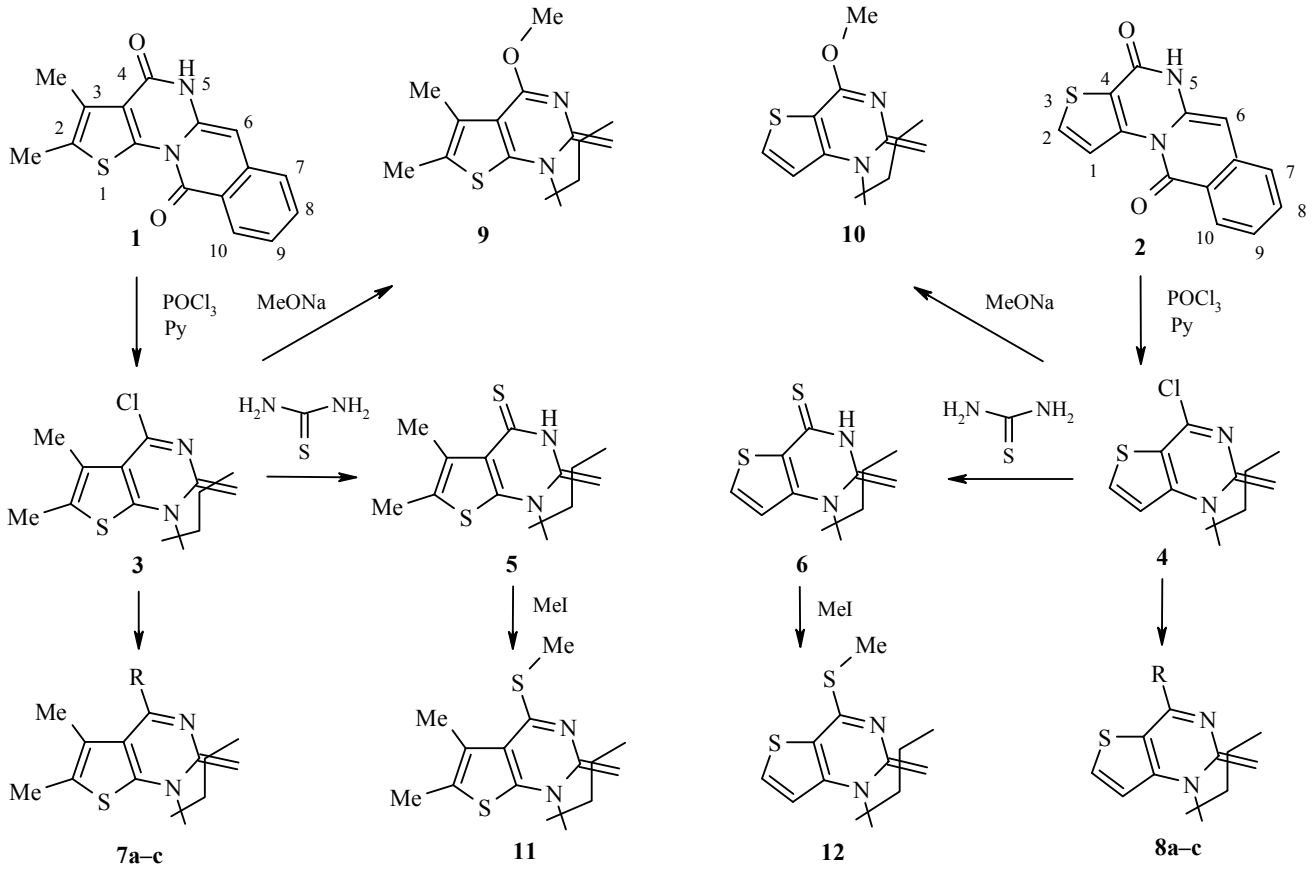

7, 8 a R = pyrrolidino, **b** R = pyperidino, **c** R = morpholino

We carried out the classical transformations of the lactam fragment into lactim or thiolactim structures as well as the former into an α-chlorimine fragment.

These transformations were achieved by treating diones **1** and **2** with $POCl_3$ in the presence of catalytic amounts of pyridine. The presence of pyridine was necessary since the yields of the desired 4-chloro derivatives **3** and **4** drop from quantitative in the presence of pyridine to 60-70% without this catalyst. The spectral characteristics of these correspond to their assigned structures. The IR spectra of chlorides **3** and **4** display no difference relative to the spectra of the starting compounds **1** and **2**, respectively, with the exception, of course, of the disappearance of the ν_{N-H} band at ~3449 cm^{-1} and appearance of the ν_{C-Cl} band at ~746 cm^{-1}. The ^1H NMR spectra of chlorides **3** and **4** show a downfield shift relative to starting compounds **1** and **2**, respectively. For example, the shift is δ 0.2-03 ppm for the aromatic protons and about 0.8 ppm for H-6 (Table 1). Bathochromic and hyperchromic effects are noted in comparing the UV spectra of **1-3** and **2-4**, respectively (the shift of the long-wavelength absorption band is 40 nm). The latter should probably be attributed to heteroaromatization of the pyrimidine part of the tetracyclic molecule as well as to the chlorine atom.

While the reaction of **3** and **4** with 2 N NaOH readily gives saponification of the chlorimine fragment and leads to isolation of the starting lactam derivatives **1** and **2**, treatment with sodium methylate in methanol also readily gives 4-methoxy derivatives **9** and **10** in yields up to 90%. Ethers **9** and **10** are inert at room temperature both toward 2 N HCl (an electrophile) and 2 N NaOH (a nucleophile). However, these compounds are partially hydrolyzed upon heating in 2 N NaOH at reflux for 8 h, gradually regenerating starting lactams **1** and **2**. The IR spectra of **9** and **10** lack the ν_{C-Cl} band at ~746 cm^{-1} characteristic for chlorides **3** and **4** but show absorption at ν_{C-H} ~2953 and ~2852 cm^{-1}. The ^1H NMR spectra of **9** and **10** display an upfield shift for the

TABLE 1. ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	H-1 (1H)	H-6 (1H, c)	H-7	H-8	H-9 (1H)	H-10 (lH, d)	Other protons
3	—	7.13	7.80 (1H, d, ^3J = 7.0)	7.87 (1H, t, ^3J = 7.5)	7.59 (t, ^3J = 7.0)	8.37 (^3J = 7.0)	2.41 (3H, s, 2-CH_3); 2.37 (3H, s, 3-CH_3)
4	8.83 (m)	7.07	7.81 (2H, m)		7.57 (m)	8.38 (^3J = 7.5)	8.23 (1H, m, H-2)
5	—	6.60	7.63 (1H, d, ^3J = 8.0)	7.71 (1H, t, ^3J = 8.0)	7.41 (t, ^3J = 7.5)	8.21 (^3J = 7.5)	2.58 (3H, s, 2-CH_3); 2.33 (3H, s, 3-CH_3); 13.15 (1H, s, 5-NH)
6	8.71 (d, ^3J = 6.0)	6.57	7.61 (1H, d, ^3J = 7.5)	7.70 (1H, t, ^3J = 7.5)	7.41 (t, ^3J = 8.0)	8.25 (^3J = 8.0)	8.20 (1H, d, ^3J = 5.5, H-2); 13.46 (1H, s, 5-NH)
7a	—	6.64	7.62 (2H, m)		7.29 (m)	8.21 (^3J = 8.5)	2.37 (3H, s, 2-CH_3); 2.34 (3H, s, 3-CH_3); 3.63 (4H, m, 4-C$\underline{H_2}$$CH_2CH_2C\underline{H_2}$–); 1.84 (4H, m, 4-$CH_2C\underline{H_2}C\underline{H_2}CH_2$–)–
7b	—	6.79	7.69 (2H, m)		7.38 (t, ^3J = 7.5)	8.26 (^3J = 8.0)	2.38 (3H, s, 2-CH_3); 2.37 (3H, s, 3-CH_3); 3.32 (4H, m, 4-C$\underline{H_2}$$(CH_2)_3C\underline{H_2}$–); 1.68 (4H, m, 4-$CH_2C\underline{H_2}CH_2C\underline{H_2}CH_2$–); 1.62 (2H, m, 4-$CH_2CH_2C\underline{H_2}CH_2CH_2$–)
7c	—	6.82	7.70 (2H, m)		7.40 (t, ^3J = 8.0)	8.26 (^3J = 8.5)	2.36 (6H, s, 2-CH_3, 3-CH_3); 3.77 (4H, m, 4-C$\underline{H_2}$$CH_2OCH_2C\underline{H_2}$–); 3.34 (4H, m, 4-$CH_2C\underline{H_2}OCH_2C\underline{H_2}$–)
9	—	6.82	7.72 (2H, m)		7.44 (m)	8.27 (^3J = 8.0)	2.32 (3H, s, 2-CH_3); 2.29 (3H, s, 3-CH_3); 4.02 (3H, s, 4-OCH_3)
8a	9.00 (d, ^3J = 6.0)	6.49	7.54 (1H, d, ^3J = 7.5)	7.59 (1H, t, ^3J = 7.5)	7.24 (t, ^3J = 7.5)	8.22 (^3J = 7.5)	8.18 (1H, d, ^3J = 5.5, H-2); 3.85 (4H, m, 4–C$\underline{H_2}$$CH_2CH_2C\underline{H_2}$–); 2.00 (4H, m, 4–$CH_2C\underline{H_2}C\underline{H_2}CH_2$–)–
8b	8.90 (d, ^3J = 5.5)	6.56	7.61 (2H, m)		7.29 (t, ^3J = 7.5)	8.25 (^3J = 8.0)	8.14 (1H, d, ^3J = 5.5, H-2); 3.89 (4H, m, 4-C$\underline{H_2}$$(CH_2)_3C\underline{H_2}$–); 1.67 (6H, m, 4-$CH_2(C\underline{H_2})_3CH_2$–)–
8c	8.92 (d, ^3J = 6.0)	6.58	7.59 (1H, d, ^3J = 7.5)	7.63 (1H, t, ^3J = 7.0)	7.31 (t, ^3J = 7.5)	8.27 (^3J = 8.0)	8.14 (1H, d, ^3J = 5.5, H-2); 3.90 (4H, m, 4-C$\underline{H_2}$$CH_2OCH_2C\underline{H_2}$–); 3.78 (4H, m, 4-$CH_2C\underline{H_2}OCH_2C\underline{H_2}$–)–
10	8.80 (m)	6.77	7.68 (2H, m)		7.43 (m)	8.32 (^3J = 6.0)	8.11 (1H, m, H-2); 4.07 (3H, s, 4-OCH_3)
11	—	6.87	7.72 (2H, m)		7.44 (t, ^3J = 7.5)	8.24 (^3J = 8.0)	2.33 (3H, s, 2-CH_3); 2.24 (3H, s, 3-CH_3); 2.53 (3H, s, 4-$SC\underline{H_3}$)–
12	8.87 (d, ^3J = 5.0)	7.05	7.79 (2H, m)		7.51 (t, ^3J = 7.0)	8.36 (^3J = 8.5)	8.15 (1H, d, ^3J = 5.0, H-2); 2.71 (3H, s, 4-SCH_3)

aromatic protons peaks in comparison with the spectra of starting chlorides **3** and **4**. An even stronger diamagnetic shift is characteristic for the methine proton at C-6 (0.3 ppm) (Table 1). Comparison of the electronic absorption spectra of compounds **9, 10** and **3, 4** shows a decrease in the HOMO-LUMO gap for the former (the shift of their long-wavelength absorption band is 30-50 nm).

The methoxy group in **9** and **10** are rather inert toward nucleophilic reagents. This is demonstrated in an experiment, in which these compounds were heated at reflux in excess pyrrolidine for 8 h. NMR spectroscopy indicated that the amount of the nucleophilic substitution products **7a** and **8a** did not exceed 10%. Amination of chlorides **3** and **4** by the same nucleophile gave the corresponding 4-amino derivatives in ~90-95% yield. This method was specifically used to obtain **7a-c** and **8a-c**. The tertiary amines have only limited solubility in 2 N HCl and are not soluble in 2 N NaOH; they are completely stable upon storage. In contrast to the IR spectra of starting compounds **3** and **4**, the spectra of **7a-c** and **8a-c** lack the ν_{C-Cl} band at ~746 cm^{-1} but show ν_{C-H} bands at ~2925 and ~2858 cm^{-1}. The ^1H NMR spectra of **7a-c** and **8a-c** show a upfield shift in comparison with the spectra of starting compounds **3** and **4**, respectively, both for the aromatic protons δ 0.10-0.15 ppm and for C(6)-H of about 0.3 ppm (Table 1).

A bathochromic shift of the long-wavelength band for the amines by 30 nm is noted in comparing the UV spectra of **7a-c, 8a-c** and **3, 4**.

No significant differences are noted in comparing the ^1H NMR spectra for **7a-9** and **8a-10** (Table 1). Comparison of the electronic absorption spectra shows a bathochromic shift of the long-wavelength band of 20 nm in going from **9** and **10** to **7a** and **8a**.

Chlorides **3** and **4** react with thiourea to give thiones **5** and **6**, which are entirely stable compounds inert both toward 2 N HCl and 2 N NaOH. In comparison with the IR spectra of starting compounds **3** and **4**, the spectra of **5** and **6** lack the ν_{C-Cl} band at ~746 cm^{-1} but display ν_{N-H} bands at ~3356 cm^{-1} and $\nu_{C=S}$ bands at ~1220 cm^{-1}, which indicates that these compounds exist in the solid state in the thione form. The ^1H NMR spectra of **5** and **6** show an upfield shift relative to starting chlorides **3** and **4** both for the aromatic protons by δ 0.10-0.15 ppm and for H-6 by about 0.5 ppm (Table 1). Comparison of the UV spectra of **3** and **4** *vs.* the spectra of **5** and **6** shows a marked bathochromic shift of the long-wavelength thione absorption of 30 nm.

Comparison of the ^1H NMR spectral characteristics of the pairs **1** *vs.* **5** and **2** *vs.* **6** shows a paramagnetic shift for **5** and **6** relative to **1** and **2**, respectively. For example, δ 0.1 ppm for the aromatic protons and about 0.3 ppm for H-6 (Table 1). Comparison of the UV spectra shows a slight bathochromic shift in going from **1** to **5** and from **2** to **6**, which is more pronounced in the case of thione **6**.

S-Methyl derivatives **11** and **12** are formed in close to quantitative yield in the methylation of thiones **5** and **6** using methyl iodide in the presence of sodium methylate. In comparison with the IR spectra of starting compounds **5** and **6**, the spectra of **11** and **12** lack the $\nu_{C=S}$ band at ~1220 cm^{-1} but show ν_{C-H} at ~2980 cm^{-1} and ν_{C-S} at ~580 cm^{-1}. The UV spectra of **11** and **12** show a marked bathochromic shift of the long-wavelength band (~20 nm) as well as a hyperchromic effect.

S-Methyl derivatives **11** and **12** are chemically inert toward 2 N NaOH and 2 N HCl but the SMe group is readily replaced by a tertiary amino group upon reactions with secondary amines. Thus, heating **11** and **12** with excess pyrrolidine at reflux for 8 h gives **7a** and **8a** in ~90% yield.

Comparison of the different spectral characteristics of **9** *vs.* **11** and of **10** *vs.* **12** shows differences introduced by the substituent at C-4 of these systems only in the case of the electronic absorption spectra of these compounds. A shift of the long-wavelength bands by 30 nm is observed in going from **9** to **11** and from **10** to **12**.

Figure 1 shows the observed changes in the electronic absorption spectra due to variation in the substituent at C-4 in the series of 11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one derivatives (**3, 7a, 9,** and **11**). The functional groups studied may be arranged in the following series Cl > SMe > NR_2 > OMe according to the effect of these groups at C-4 on the position of the long-wavelength absorption band. The smallest gap between the HOMO and LUMO is found for the chlorine atom (chloride **3**).

Figure 2 also reflects the same changes but in the series of 11H-thieno[2',3':5,6]pyrimido-[1,2-*b*]isoquinolinones (**4, 8a-c, 10, 12**). A slight inversion of the position of the long-wavelength absorption band is observed for these compounds and the series is somewhat different: SMe > Cl > NR_2 > OMe.

The changes in the long-wavelength absorption observed in Figs. 1 and 2 are a function of mesomeric, inductive, and steric effects of the unshared electron pair of the "polar" atom of the replacement group (nitrogen, oxygen, or sulfur) at C-4 in the quasiaromatic system resonance.

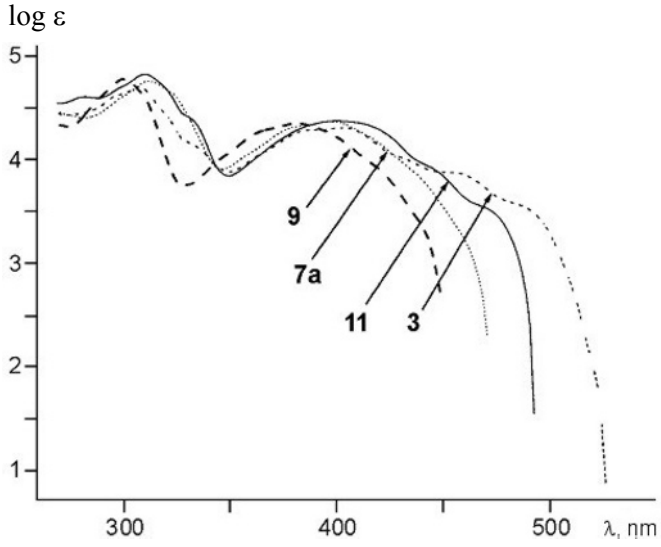

Fig. 1. UV spectra of compounds **3, 7a, 9,** and **11.**

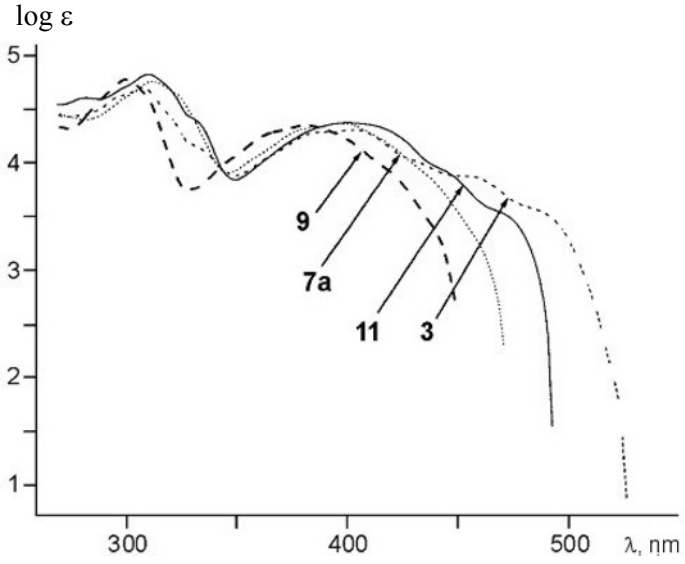

Fig. 2. UV spectra of compounds **4, 8a, 10,** and **12.**

Analysis of the physicochemical characteristics to reveal their differences in the positional isomers in the series of 4-substituted 11H-thieno[3',2':5,6]- and 11H-thieno[2',3':5,6]pyrimido[[1,2-*b*]isoquinolin-11-ones showed that the IR and NMR spectra are unsuitable for these purposes since they are highly similar. UV spectroscopy is the major method, which can be used to demonstrate significant differences for the positional

TABLE 2. Estimated Biological Activity of Compounds Synthesized

Compound	A type of biological activity	P_a	P_i
6	*Agonist of dopamine D_4 receptors*	0.895	0.006
8a		0.910	0.005
8b		0.910	0.005
8c		0.882	0.006
10		0.897	0.006
12		0.897	0.006

isomers. In all the compared pairs of UV spectra (**9** vs. **10**, **7a-c** vs. **8a-c**, **5** *vs.* **6**, and **11** *vs.* **12**), we found a bathochromic shift of the long-wavelength absorption band of about 20-25 nm in comparison with their positional isomers. An exception was found for the pair of 4-chloro derivatives (**3** *vs.* **4**). Here, similar gaps between the HOMO and LUMO were found in the UV spectrum.

The biological activity spectrum was calculated for the compounds studied. The PASS (Prediction of Activity Spectrum for Substances) program [19, 20] was used for these studies. The activity threshold was taken as $P_a > 0.85$ and $P_i < 0.20$. Among the positional isomers, derivatives **6, 8a-c, 10,** and **12** were found to have the greatest pharmacological potential in the series of 11H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-ones (see Table 2).

A high level of activity relative to D_4 dopamine receptors is projected for all these compounds, which should act as agonists toward these receptors [21]. Derivatives **8a** and **8b** deserve special attention in this regard.

EXPERIMENTAL

The melting points of the compounds synthesized were measured in Pyrex capillaries on a Thiele apparatus and not corrected. The purity of the products was demonstrated using an Agilent 1100 Series mass chromatograph with an Agilent LC/MSD SL selective detector. The sample was introduced in a matrix of trifluoroacetic acid and subjected to electron impact ionization. The *m/z* values of the $[M+1]^+$ molecular ion peaks are given. The chromatographic mobility of products **3-10** on Merck 60 F_{254} plates is somewhat lower ($R_f \sim 70$-75) than for the starting compounds **1** and **2** ($R_f \sim 85$) using 9:1 benzene–methanol as the eluent.

The ^{1}H NMR spectra were taken in DMSO-d_6 on a Varian Unity Plus 400 spectrometer at 400 MHz for compound **4** and a Bruker Avance DRX 500 spectrometer at 500 MHz using TMS as the internal standard. The IR spectra were taken on a Nicolett-470 Nexus spectrometer for KBr Pellets. The UV spectra were taken for $5 \cdot 10^{-5}$ M solutions of the compounds in DMF on a Perkin-Elmer UV-vis Lambda 20 spectrometer.

2,3-Dimethyl-5,11-dihydro-4H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinoline-4,11-dione (1). A. Dione **1** was obtained with mp 325°C according to Cheng [12].

B. Compound **3** (0.314 g, 1 mmol) was heated in 2 N NaOH (20 ml) at reflux for 2 h and cooled. The precipitate was filtered off and washed with water to give dione **1** in ~90% yield. A mixed probe with a sample obtained by method A did not give a depressed melting point.

5,11-Dihydro-4H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinoline-4,11-dione (2). A. Dione **2** was obtained according to Cheng [12]; mp 290°C.

B. A sample of compound **4** (0.286 g, 1 mmol) was heated at reflux for 2 h in 2 N NaOH (20 ml) and cooled. The precipitate was filtered off and washed with water to give dione **2** in ~90% yield. A mixed probe with a sample obtained by method A did not give a depressed melting point.

4-Chloro-2,3-dimethyl-11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (3). A mixture of compound **1** (2.96 g, 10 mmol), phosphorus oxychloride (15.3 ml, 25.62 g, 167 mmol), and dry pyridine (1.53 ml) was heated at reflux for 90 min, cooled, and poured into ice water. Then, 25% ammonium hydroxide was added to bring the mixture to pH 4. The precipitate was filtered off and washed with water to give 3.1 g (98.4%) chloride **3** as yellow crystals; mp 235°C (DMF). IR spectrum, ν, cm^{-1}: 1664 (C=O), 1575 (C=N), 1533, 1463, 1432, 1220, 1149, 1020, 746 (C–Cl), 686. Mass spectrum, *m/z*: 315 [M^++1]. Found, %: C 61.00; H 3.48; Cl 11.48; N 8.82; S, 10.24. $C_{16}H_{11}ClN_2OS$. Calculated, %: C 61.05; H 3.52; Cl 11.26; N 8.90; S 10.19.

4-Chloro-11H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (4). A mixture of compound **2** (2.68 g, 10 mmol), phosphorus oxychloride (15.3 ml, 25.62 g, 167 mmol), and dry pyridine (1.53 ml) was heated at reflux for 90 min, cooled, and poured into ice water. Then, 25% ammonium hydroxide was added to bring the mixture to pH 4. The precipitate was filtered off and washed with water to give 2.81 g (98.4%) chloride **4** as red-brown crystals; mp 200°C (DMF). IR spectrum, ν, cm^{-1}: 1664 (C=O), 1571 (C=N), 1546, 1475, 1425, 1392, 1083, 995, 817, 748 (C–Cl), 675. Mass spectrum, *m/z*: 287 [M^++1]. Found, %: C 58.45; H 2.51; Cl 12.28; N 9.86; S 11.24. $C_{14}H_7ClN_2OS$. Calculated, %: C 58.64; H 2.46; Cl 12.36; N 9.77; S 11.18.

2,3-Dimethyl-4-thioxo-5,11-dihydro-4H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (5). Compound **3** (3.14 g, 10 mmol) was added to a solution of thiourea (0.84 g, 11 mmol) in ethanol (40 ml). The mixture was heated at reflux for 210 min and cooled. The precipitate was filtered off to give 2.98 g (95.5%) compound **5** as orange crystals; mp 290°C (DMSO). IR spectrum, ν, cm^{-1}: 3356 (N–H), 3302, 1670 (C=O), 1614, 1596, 1560 (C=N), 1489, 1456, 1430, 1350, 1211 (C=S), 688. Mass spectrum, *m/z*: 313 [M^++1]. Found, %: C 61.48; H 3.92; N 9.03; S 20.67. $C_{16}H_{12}N_2OS_2$. Calculated, %: C 61.51; H 3.87; N 8.97; S 20.53.

4-Thioxo-5,11-dihydro-4H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (6). Chloride **4** (2.86 g, 10 mmol) was added to a solution of thiourea (0.84 g, 11 mmol) in ethanol (40 ml). The mixture was heated at reflux for 210 min and cooled. The precipitate was filtered off to give 2.70 g (95.0%) compound **6** as yellow crystals; mp 320°C (DMSO). IR spectrum, ν, cm^{-1}: 3403 (N–H), 1662 (C=O), 1618, 1601, 1562 (C=N), 1444, 1396, 1232 (C=S), 1022, 746. Mass spectrum, *m/z*: 285 [M^++1]. Found, %: C 59.21; H 2.90; N 9.90; S 22.52. $C_{14}H_8N_2OS_2$. Calculated, %: C 59.13; H 2.84; N 9.85; S 22.55.

4-Methoxy-2,3-dimethyl-11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (9). Chloride **3** (3.14 g, 10 mmol) was added to a solution of sodium methylate prepared from metallic sodium (0.34 g, 14.8 mmol) and methanol (45 ml), heated at reflux for 6 h, and cooled. The precipitate was filtered off to give 2.79 g (90%) compound **9** as colorless crystals; mp 205°C (DMF). IR spectrum, ν, cm^{-1}: 2918, 2852 (C–H), 1655 (C=O), 1588, 1536 (C=N), 1501, 1473, 1439, 1415, 1346, 1330, 1306, 1286, 1172, 1150 (C–O), 990, 748, 612. Mass spectrum, *m/z*: 311 [M^++1]. Found, %: C 65.83; H 4.62; N 9.10; S 10.51. $C_{17}H_{14}N_2O_2S$. Calculated, %: C 65.79; H 4.55; N 9.03; S 10.33.

2,3-Dimethyl-4-tetrahydro-1H-1-pyrrolyl-11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (7a). A. Pyrrolidine (2.5 ml, 2.13 g, 30 mmol) was added to a suspension of chloride **3** (3.14 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.36 g (96.2%) compound **7a** as yellow crystals; mp 190°C (DMSO).

B. Compound **11** (0.326 g, 1 mmol) was heated at reflux for 8 h in pyrrolidine (20 ml) and cooled. The precipitate was filtered off and washed with water to give compound **7a** in ~90% yield. A mixed probe with a sample prepared by method A did not give a depressed melting point. IR spectrum, ν, cm^{-1}: 2925, 2883 (C–H), 1648 (C=O), 1583, 1568 (C=N), 1517, 1456, 1411, 808. Mass spectrum, *m/z*: 350 [M^++1]. Found, %: C 68.82; H 5.52; N 11.98; S 9.24. $C_{20}H_{19}N_3OS$. Calculated, %: C 68.74; H 5.48; N 12.02; S 9.18.

2,3-Dimethyl-4-piperidino-11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (7b). Piperidine (3 ml, 2.55 g, 30 mmol) was added to a suspension of chloride **3** (3.14 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.48 g (96%) compound **7b** as yellow crystals; mp 180°C (DMSO). IR spectrum, ν, cm^{-1}: 2927, 2856 (C–H), 1655 (C=O), 1587, 1572 (C=N), 1523, 1463, 1417. Mass spectrum, *m/z*: 364 [M^++1]. Found, %: C 69.48; H 5.78; N 11.63; S 8.93. $C_{21}H_{21}N_3OS$. Calculated, %: C 69.39; H 5.82; N 11.56; S 8.82.

2,3-Dimethyl-4-morpholino-11H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (7c). Morpholine (2.65 ml, 2.61 g, 30 mmol) was added to a suspension of chloride **3** (3.14 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.50 g (96%) compound **7c** as yellow crystals; mp 230°C (DMSO). IR spectrum, ν, cm^{-1}: 2966, 2858 (C–H), 1645 (C=O), 1583, 1570 (C=N), 1525, 1466, 1419, 1248, 1119 (C–O). Mass spectrum, *m/z*: 366 [M^++1]. Found, %: C 65.86; H 5.32; N 11.61; S 8.83. $C_{20}H_{19}N_3O_2S$. Calculated, %: C 65.73; H 5.24; N 11.50; S 8.77.

4-Methoxy-11H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (10). Chloride **4** (2.86 g, 10 mmol) was added to a solution of sodium methylate prepared by adding metallic sodium (0.34 g, 14.8 mmol) to methanol (45 ml). The mixture was heated at reflux for 6 h and cooled. The precipitate was filtered off to give 2.54 g (90%) compound **10** as colorless crystals; mp 165°C (DMSO). IR spectrum, ν, cm^{-1}: 2993, 2953 (C–H), 1660 (C=O), 1593, 1558 (C=N), 1527, 1479, 1469, 1445, 1352, 1180, 1151 (C–O), 1125, 1085, 1025, 948, 822, 760, 633, 616. Mass spectrum: 283 [M^++1]. Found, %: C 63.92; H 3.62; N 10.02; S 11.28. $C_{15}H_{10}N_2O_2S$. Calculated, %: C 63.82; H 3.57; N 9.92; S 11.36.

4-Tetrahydro-1H-1-pyrrolyl-11H-thieno[2'3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (8a). A. Pyrrolidine (2.5 ml, 2.13 g, 30 mmol) was added to a suspension of chloride **4** (2.86 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.11 g (97%) compound **8a** as orange crystals; mp 232°C (DMSO).

B. Compound **12** (0.298 g, 1 mmol) in pyrrolidine (20 ml) was heated at reflux for 8 h and cooled. The precipitate was filtered off to give compound **8a** in ~90% yield. A mixed probe with a sample prepared by Method A did not give a depressed melting point. IR spectrum, ν, cm^{-1}: 2956, 2869 (C–H), 1649 (C=O), 1566, 1552 (C=N), 1495, 1464, 766. Mass spectrum, *m/z*: 322 [M^++1]. Found, %: C 67.32; H 4.64; N 13.12; S 10.04. $C_{18}H_{15}N_3OS$. Calculated, %: C 67.27; H 4.70; N 13.07; S 9.98.

4-Piperidino-11H-thieno[2',3':5,6]pyrimido[1, 2-*b*]isoquinolin-11-one (8b). Piperidine (3 ml, 2.55 g, 30 mmol) was added to a suspension of chloride **4** (2.86 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.25 g (97%) compound **8b** as orange crystals; mp 200°C (DMSO). IR spectrum, ν, cm^{-1}: 2926, 2858 (C–H), 1653 (C=O), 1591, 1562 (C=N), 1460, 765. Mass spectrum, *m/z*: 336 [M^++1]. Found, %: C 68.12; H 5.17; N 12.58; S 9.63. $C_9H_{17}N_3OS$. Calculated, %: C 68.04; H 5.11; N 12.53; S 9.56.

4-Morpholino-11H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (8c). Morpholine (2.65 ml, 2.61 g, 30 mmol) was added to a suspension of chloride **4** (2.86 g, 10 mmol) in absolute ethanol (20 ml). The mixture was heated at reflux for 9 h and cooled. The precipitate was filtered off to give 3.24 g (96%) compound **8c** as yellow crystals; mp 230°C (DMSO). IR spectrum, ν, cm^{-1}: 2958, 2852 (C–H), 1655 (C=O), 1614, 1593, 1556 (C=N), 1491, 1466, 1113 (C–O), 758. Mass spectrum, *m/z*: 338 [M^++1]. Found, %: C 64.12; H 4.52; N 2.52; S 9.54. $C_{18}H_{15}N_3O_2S$. Calculated, %: C 64.08; H 4.48; N 12.45; S 9.50.

2,3-Dimethyl-4-methylsulfanil-1H-thieno[3',2':5,6]pyrimido[1,2-b]isoquinolin-11-one (11). Compound **5** (3.12 g, 10 mmol) was added to a solution of sodium methylate prepared from metallic sodium (0.24 g, 11 mmol) and methanol (75 ml). Then, methyl iodide (0.65 ml, 1.42 g, 10 mmol) was added and stirred at room temperature for 2 h. The precipitate was filtered off and washed with 5% aqueous sodium bicarbonate and water to give 3.10 g (95%) compound **11** as yellow crystals; mp 182°C (DMSO). IR spectrum, ν, cm^{-1}: 2925, 2850 (C–H), 1653 (C=O), 1614, 1587, 1570 (C=N), 1518, 1460, 1432, 1219, 1147, 1026, 688 (C–S). Mass spectrum, *m/z*: 327 [M^++1]. Found, %: C 62.57; H 4.28; N 8.65; S 19.68. $C_{17}H_{14}N_2OS_2$. Calculated, %: C 62.55; H 4.32; N 8.58; S 19.64.

4-Methylsulfanil-11H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinolin-11-one (12). Compound **6** (2.84 g, 10 mmol) was added to a solution of sodium methylate prepared from metallic sodium (0.24 g, 11 mmol) and methanol (75 ml). Then, methyl iodide (0.65 ml, 1.42 g, 10 mmol) was added and the mixture was stirred at room temperature for 2 h. The precipitate was filtered off and washed with 5% aqueous sodium bicarbonate and water to give 2.83 g (95%) compound **12** as orange crystals; mp 150°C (DMSO). IR spectrum,

ν, cm^{-1}: 2925 (C–H), 1662 (C=O), 1618, 1595, 1541 (C=N), 1471, 1421, 1006, 748, 677 (C–S). Mass spectrum, *m/z*: 299 [M^++1]. Found, %: C 60.44; H 3.40; N 9.40; S 21.38. $C_{15}H_{10}N_2OS_2$. Calculated, %: C 60.38; H 3.38; N 9.39; S 21.49.

All the products synthesized are available at the address: www.enamine.net.

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